REMARKS

The pending claims

Claims 21, 24, 26, 30, and 36-39 are currently pending and under examination. The remaining claims stand canceled.

The 35 USC § 103 rejections

Claims 21, 24, 26, 30, and 36-39 were rejected under 35 USC § 103(a) as allegedly obvious over Chamberlain et al. (US 2005/023083 A1) in view of Klaviniskis et al. (US 2003/014792) and Ryan (US 4,171,353). This rejection is respectfully traversed. Reconsideration and withdrawal of the rejection in view of the following remarks is respectfully requested.

As an initial matter, Applicants wish to clarify this statement from the Office Action:

> **The instant claims are directed to a composition comprising a SMIP compound of formula XXI and an antigen in an oil-in-water emulsion.**

Applicants respectfully point out that only claim 39 recites an oil-in-water emulsion adjuvant. The pending claims are directed to compositions comprising a SMIP (Small Molecule Immune Potentiator) compound of formula XXI and an antigen wherein the benzazole compound of formula XXI acts as an adjuvant and is present in an amount effective to enhance the subject's immune response to the antigen. Claim 21 does not recite or require an oil-in-water emulsion, and claim 39 expressly adds a *second* adjuvant that is an oil-in-water emulsion adjuvant.

Applicants will now address the rejections beginning with the cited references.

Chamberlain et al . US 2005/023083 A1

Chamberlain et al. discloses certain benzimidazole compounds for treating disorders mediated by VEGFR-2 and TIE-2 kinases and those relating to angiogenesis, such as cancer. Applicants agree with the Office Action that Chamberlain et al. does not disclose antigens. Moreover, Chamberlain *et al.* also does not disclose any teachings that the benzimidazole compounds can serve as an adjuvant in a composition or induce an immune response.

It is important to note, too, that Chamberlain was not shown to disclose or suggest that the compounds it discusses have activity as SMIPs. They appear to be disclosed solely for direct treatment of "diseases associated with inappropriate angiogenesis." (Chamberlain, para. [0001]) Accordingly, not only does the reference fail to disclose an antigen in combination with these compounds, it also offers no reason to combine its compounds with an antigen or to use them in any vaccine-like composition.

The Examiner noted that the term 'vaccine' is in the preamble of the present claim, and thus may be given little weight. However, the claim expressly indicates that the benzazole compound "is present in an amount effective to enhance the immune response" to an antigen. The "immune response" is a claim limitation that links the text of the claim to the preamble. It is clear that the presence and the amount of the benzazole compound are associated with the effectiveness of the composition for eliciting an immune response, which is the purpose of the antigen. Accordingly, the fact that the composition is a vaccine composition should not be lightly dismissed: the purpose of the compound in the composition is to act as a SMIP, which the Examiner acknowledged, not to function as a therapeutic agent; and the composition as claimed is useful because of the SMIP effect of the compound in combination with the antigen.

The Office Action states that paragraph [0394] of Chamberlain discloses pharmaceutical oil-in-water emulsions. This was used as a rationale for combining Chamberlain's compounds with the compositions in Klaviniskis: the Office asserts that Chamberlain's oil-in-water emulsions would act as vaccine adjuvants for use with antigens from Klaviniskis (discussed

below). Applicants note that the emulsions taught in paragraph [0394] of Chamberlain are expressly ones for oral administration: "**Pharmaceutical formulations adapted for oral administration may be presented as ...oil in water liquid emulsions or water-in-oil liquid emulsions.**" Thus Chamberlain teaches use of oil in water liquid emulsions as pharmaceutical carriers for the oral administration of the benzimidazole compounds. It does not disclose oil-in-water emulsions that are vaccine adjuvants, or indicate that the emulsions it describes generically and for oral delivery would act as vaccine adjuvants. Even claim 39 herein expressly indicates that it refers to an 'oil-in-water' adjuvant, not just to any oil-in-water composition. Chamberlain provides no disclosure or suggestion of such an adjuvant.

A person of ordinary skill, upon reading the relevant passage in Chamberlain, would not have expected the oral therapeutic formulations it so briefly mentioned to be useful in a vaccine composition or to function as an adjuvant. As Ryan (US Patent No. 4,171,353, further discussed below) says, oil-in-water adjuvants are known; but that does not mean that every 'oil-in-water' composition is useful as an adjuvant. Chamberlain does not mention oil-in-water adjuvants for immunological compositions, and it is improper to infer that the general term 'oil-in-water' used to describe an oral formulation is related to an 'oil-in-water adjuvant' from Ryan, which is clearly disclosed for injections. Ryan, col. 1, lines 26-44, describing these as a type of 'repository adjuvants'.

Klaviniskis et al. US 2003/0147923

The Examiner acknowledges that Chamberlain does not disclose antigens, but relies upon Klaviniskis to address the deficiency of Chamberlain et al. The Office Action states:

> **Klaviniskis et al. disclose a composition comprising spores of Bacillus subtilis as a method of stimulating immune responsiveness in a subject. The spores have an adjuvant, immunomodulatory, immune potentiation effect in a subject (abstract). Klaviniskis et al. also disclose that antigens can be used as adjuvant in the present composition (pg. 15, section 0155) to boost an immune response in a mammal**

(abstract). In addition to the MF59 adjuvant (pg. 2, section 0014), other antigens that are mentioned to be useful are influenza, hemagglutinin, and neuraminidase (pg. 14, section 0147). Furthermore, Klaviniskis et al. disclose the present compositions can be used to treat colon and breast cancers (pg. 7, section 0082-0083).

First, the Applicants respectfully point out that Klaviniskis says "antigens can be used as adjuvant in the present compositions (pg. 15, section 0155)." The cited paragraph discloses that "the spores themselves can be used...as an adjuvant..." It defines adjuvant as "a compound that acts in a non-specific manner to augment specific immunity (e.g., an immune response) to an immunomodulatory molecule, such as, for example, an immunologenic polypeptide or peptide or antigen..." It does *not* disclose or suggest that an 'antigen' acts as an adjuvant, only that the Bacillus spores as an adjuvant can be used *along with* an antigen. Thus it provides no reason to combine the spores from Klaviniskis (which are described as adjuvants, and have no disclosed therapeutic activity at all in the absence of an added antigen) with the compounds of Chamberlain, which are indicated to be therapeutic but not antigenic. The spores do not provide anticancer effects without an antigen present; and the compounds of Chamberlain are not indicated to be useful as antigens. Thus there is no reason to add spores from Klaviniskis to the Chamberlain compounds, nor is there any evident reason to add an antigen from Klaviniskis to the Chamberlain compounds.

Second, the Applicant does not agree that there is any motivation to combine Chamberlain with vaccine-related compositions of any sort. Chamberlain does not indicate any reason to do so. The Office Action cites a section where Chamberlain mentions use of its compounds with other agents, such as other cancer therapeutics. According to the Examiner, "other therapeutic agents may be employed in combination with the disclosed compounds. In particular, in anti-cancer therapy, combination with other chemotherapeutic, hormonal or antibody agents is envisaged (section 0414)." Notably, none of the 'other therapeutic agents' that

Chamberlain contemplates is an immunological composition: none of these 'therapeutic agents' would be expected to work by eliciting an immune response. Chamberlain does not provide any reason to combine its compounds with any antigen or to include them in a vaccine-like composition.

In addition, even if such compositions were to be used with the compounds from Chamberlain, the cited passage from Chamberlain does not indicate that such other therapeutic agents would be combined with its compounds into a single composition. It is well known in the art that a vaccine composition is not generally combined with therapeutic agents. The obviousness analysis in the Office Action relies heavily upon the supposition that one of ordinary skill would have been motivated to mix a therapeutic agent taught in Chamberlain with an immunogenic composition of Klavinskis, even though the therapeutic compound of Chamberlain was only said to be useful with other therapeutic agents. Chamberlain clearly does not indicate that its compounds have any place in a vaccine, or in a mixture with an antigen. Applicants respectfully assert that the combination of these two references is improper in the absence of a reason for the Chamberlain compounds to be physically combined with a vaccine composition or admixed with an antigen. The Examiner has not provided evidence that a person of ordinary skill would routinely combine a vaccine with a therapeutic agent: the very general statement in Chamberlain cannot be construed to support such combinations, when it uses the term 'therapeutic agent' and does not suggest any preventive or immunogenic compositions.

Klaviniskis et al. discloses on pg. 7, section 0082-0083 that the spores can be used in a *method* wherein the spores are administered with cancer vaccine components and in combination with an anti-cancer agent. However, Klaviniskis et al. does *not* teach a single composition comprising the spores, vaccine components, and an anti-cancer agent.

Ryan US Patent 4,171,353

In the description of the prior art, Ryan describes known adjuvants as including oil-in-

water type adjuvants that operate by slowly releasing the antigen from the oil emulsion, and their advantages over the more common aluminum adjuvants (alum). A careful reading of that passage makes it clear that these are for injection: it describes them as 'repository adjuvants' that provide slow release of antigen, and discusses injection site problems. Ryan, col. 1, lines 26-44. The Office Action relies on the slow release of antigen noted by Ryan to support the assertion that:

> **Therefore it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed invention was made, to combine the antigens as taught by Klaviniskis et al with the oil-in-water emulsion composition taught by Chamberlin et al.**

Applicants disagree that this combination would be *prima facie* obvious because 1) Chamberlain's general reference to 'oil-in-water' formulations does not disclose or suggest an oil-in-water adjuvant, 2) Chamberlain does not suggest using oil-in-water formulations for injections, 3) Ryan only suggests using oil-in-water adjuvants for injection, and 4) Ryan teaches away from the use of the peptide antigens taught in Klaviniskis for oral administration.

First, 'oil in water' is a generic term that can encompass a wide variety of materials, including salad dressings. This broad, generic term cannot be interpreted to mean the same thing in every context. In particular, the emulsion of Ryan are not indicated to be the same as the emulsions of Chamberlain et al. Ryan teaches that some common oil emulsion are adjuvants for vaccine *injections* (see col 1 line 34-35 **"By virtue of this insolubilization, the antigen is thereafter released more slowly from the site of injection"** and Col 1 lines 41-42 **"is more likely to produce nodules and abscesses at the site of injection…**). The emulsions taught by Chamberlain et al. however are ones for *oral administration* and thus are used merely as carriers, rather than as adjuvants. They do not serve the same purpose as emulsions in Ryan, so there is no basis to assume they have the same composition or the same effect. The fact that one is for injection and the other for oral administration is further evidence that it is not reasonable to assume they are the same.

In addition, Chamberlain et al. teaches only oral administration of emulsions, and the tumor antigens of Klaviniskis et al. are polypeptides. These peptide antigens could not be effectively administered orally as they would be expected to be destroyed by the digestive tract and/or proteases before entering the bloodstream, and may well antagonize immune responses. Indeed, Ryan teaches away from using oral administration of a peptide immunogen with existing adjuvants, including the oil-in-water adjuvants that it acknowledges as prior art. Ryan teaches that "it has not heretofore been possible to administer the [protein] antigens with any of the known adjuvants orally and obtain both an oral and systemic immunity." Ryan, col. 1, lines 50-56. Ryan further says that oral immunization with protein antigens inhibits immune responses rather than eliciting immunity. Ryan, col. 1, lines 60-67. In view of Ryan's teaching about oral delivery of immunogenic peptides, one would not have been motivated to use Chamberlain's oral oil-in-water formulations to elicit an immune response with the peptidic antigens from Klaviniskis. The combination would not have been expected to work.

The Office Action further states that:

> **A person of ordinary skill in the art would have been motivated to combine the antigens as taught by Klaviniskis et al. with the oil-in-water emulsion composition as taught by Chamberlain et al. because (1) Chamberlain and Klaviniskis et al. are analogous art since both disclose a method of treating colon and breast cancers; (2) Chamberlain et al. teaches that other therapeutic agents may be employed in anti-cancer therapy; (3) Klaviniskis et al. disclose a composition comprising spores, which contain adjuvants that have an immunomodulatory effect and stimulates immune responsiveness; and (4) Chamberlain et al. discloses oil-in-water emulsion, which are well-known immunological adjuvants that provide slow release of the antigen. Therefore one of ordinary skill in the art would have had a reasonable expectancy to successfully make a composition comprising the active agent disclosed by Chamberlain et al. and the antigen and adjuvant disclosed by Klaviniskis, that would effectively treat colon and breast cancers by stimulating the**

immune system and enhancing an immune response, while providing slow release of the antigen.

As discussed above, Chamberlain et al. does not teach antigens, does not teach oil-in-water emulsion adjuvants or describe emulsions that are suitable for injection, and thus does not provide motivation to combine its compounds with either antigens or vaccine adjuvants in a single composition. Ryan teaches away from using an 'oral' oil-in-water formulation for inducing an immune response to a peptide antigen. Klaviniskis et al. teaches some antigens, but the only antigens relating to the treatment of cancer appear to be polypeptides, and these would not be expected to be deliverable according to the oral formulation of Chamberlain et al. as an oil-in-water emulsion—as expressly recognized by Ryan.

The Office Action closes its arguments by citing *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). The court's opinion in *Kerkhoven* states:

> **It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form third composition which is to be used for the very same purpose...the idea of combining them flows logically from their having been individually taught in the prior art. In the case at bar, appealed claims...require not more than the mixing together of two conventional spray-dried detergents. Thus these claims set forth prima facie obvious subject matter.**

Applicants respectfully assert that *Kerkhoven* is inapplicable to the present situation. *Kerkhoven's* reference to two compositions being "used for the very same purpose" is an important distinction from the present facts. *Kerkhoven* related to combining different materials where each was known to act as a detergent. However, Chamberlain discloses compounds to inhibit angiogenesis. Klaviniskis discloses compositions to elicit immunological responses. Each is generally useful in principle for treating cancer, but since they operate in vastly different ways, raise very different issues of timing and routes of administration. Therapeutic treatment

and vaccination / immune response development are just not the same purpose. Nothing in Chamberlain indicates that its compounds or compositions are useful for the purpose of the immunological compositions discussed in Klaviniskis.

Chamberlain's compositions are used to inhibit angiogenesis; Klaviniskis' compositions are used to induce an immune response. The fact that both references refer generally to methods of treating cancers does not mean that their compositions would ever be combined; at most, it suggests that both could be used in a single subject having cancer.

In re Geiger, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987) teaches that there is no presumption of obviousness in combinations merely because two items could be employed for the same general methods ("Based upon the prior art and the fact that each of the three components of the composition used in the claimed method is conventionally employed in the art for treating cooling water systems, the board held that it would have been *prima facie* obvious, within the meaning of 35 U.S.C. 103, to employ these components in combination for their known functions and to optimize the amount of each additive.... Appellant argues... hindsight reconstruction .... We agree with appellant.").

Like the situation in *In re Geiger*, the 'use' here is such a broad and general one that it does not suggest combining the materials from the separate references into a single composition. The considerations required for combination of pharmaceutical compositions are vastly different from those for the simple combination of detergents, which is what was addressed in *Kerkhoven*. It is well know that the formulation of drugs and the determination of their mode of administration and dosing schedules must take into account many factors including drug toxicities, tolerability, efficacy, and bioavailability. Just because two drugs could both be used in methods to treat a common disorder does not provide motivation to combine the two in a single composition, in view of the expected differences in dosages, frequency and timing, route of administration, dietary effects, etc. Even more clearly, just because immunological composition "A" could be used for a type of cancer, and drug "B" could be used for the same type of cancer,

the person of ordinary skill would not expect to be able to combine "A" and "B" into a single, useful composition that provide the immunological effects and the therapeutic effects of both.

The Examiner is invited to provide evidence to show that persons of ordinary skill would have considered it reasonable to combine a cancer therapeutic that acts by inhibition of angiogenesis with an immunological composition having anticancer effects; however, in the absence of such evidence, no *prima facie* case for obviousness is established for a combination composition, merely because two disparate types of compositions that are *known* to work in very different ways could both be used for the very general concept of treating cancer.

With regard to the *Graham* factors: step one in the *Graham* analysis involves determining the scope and content of the prior art. Contrary to the Examiner's position, the references do not both disclose oil-in-water adjuvants. The mention of 'oil-in-water' from Chamberlain refers to an emulsion used as a carrier for oral administration of a drug. It does not disclose or suggest an oil-in-water adjuvant. Nor has the Examiner provided rationale to show that it would necessarily have the properties of an adjuvant. Ryan discusses oil-in-water adjuvants—note that the two references use different terms, and they describe compositions having different purposes. The two references cannot be presumed to mean the same thing when they have in common such a general term as 'oil in water'. The generic term 'oil-in-water' does not establish any relationship between Chamberlain's oral formulations and the immunological compositions from Ryan; it cannot provide motivation to combine the unrelated materials into a single composition. This unfounded presumption by the Examiner is a basis for the rejection, and it misinterprets the scope and content of the prior art. Thus it does not support an obviousness rejection under the *Graham* analysis.

With respect to the differences between the claims and the prior art: for one, the claims provide a composition wherein a SMIP of specified formula is used as an adjuvant to enhance an immune response, and is thus combined with an antigen. The prior art discloses neither the usefulness of the specified formula as a SMIP, nor any composition where it is combined with an antigen. The prior art does not disclose a combination of Chamberlain's compounds with an

antigen, as the Examiner acknowledged; and no proper basis to combine a compound from Chamberlain with an antigen has been shown. Accordingly, no prima facie obviousness rejection has been established

Objective Evidence of Nonobviousness

In addition, even if a *prima facie* case of obviousness were established, it can be overcome by evidence of nonobviousness. *See Graham.* In combining Chamberlain's compounds with immunological compositions from Klaviniskis, the examiner relies, albeit improperly, upon mention of 'oil-in-water' compositions in Chamberlain, or upon the spores mentioned as adjuvants in Klaviniskis, to elicit an adequate immune response to the antigen. The present compositions do not rely upon known adjuvants: they take advantage of the heretofore unknown adjuvant effect of the SMIP compounds included in claim 21. The SMIP compound provides an effect in combination with an antigen (which combination was NOT in the prior art) that would not have been expected: it enhances the immune response elicited by the antigen. Thus the claimed composition, which contrary to the rationale for the rejection does not require an adjuvant, provides an effect that would not have been expected without an adjuvant. The composition as claimed would not have been expected to operate as an effective immunological composition: it would have needed an adjuvant. The Examiner pulled one in from the specification or cited references *because a person of ordinary skill would have expected to need an adjuvant*; however, the composition as claimed does not need one. It is unexpectedly effective without an adjuvant: this overcomes any alleged basis for an obviousness rejection.

In addition, Ryan expressly teaches away from oral administration of peptide antigens with oil-in-water emulsions, which is the combination that the Examiner seems to rely upon for the rejection, which is said to use the "oil in water emulsions taught by Chamberlain." Clear teaching away in the art rebuts a *prima facie* case for obviousness, because it demonstrates that one of ordinary skill would not have expected this combination as claimed to work—even if the compound from Chamberlain were used as an 'oil-in-water' emulsion, which is not what claim 21 recites.

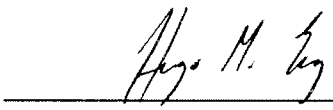
In summary, Chamberlain discloses compounds with therapeutic uses, but no connection with immunological compositions. Even if interpreted to suggest combining the use of its compounds with the use of immunological compositions from Klaviniskis, that does not establish a *prima facie* basis for combining those materials into a single composition. The person of ordinary skill would not be expected to combine an immunological composition from Klaviniskis with a therapeutic one from Chamberlain to make a single composition—their purposes and functions are just too different. If combined into a single composition as claimed in claim 21, the person of ordinary skill would not have expected the combination to elicit an immunological response without addition of another material, an adjuvant, because the adjuvant effect of the compound in claim 21 was not known and thus could not have been expected. Thus a person of ordinary skill would not have arrived at the composition of claim 21, and would not have expected it to work. Moreover, the particular combination in the rejection, using Chamberlain's oil-in-water oral formulations for its compounds plus an antigen from Klaviniskis, would not address the deficiency because the oil-in-water composition in Chamberlain is not necessarily an adjuvant, so it does not inherently possess the necessary characteristics to make the combination work, and because Ryan teaches away from using an oil-in-water formulation for oral delivery of the type of antigens Klaviniskis mentions. Plus, of course, the invention as claimed does not include the oil-in-water formulation from Chamberlain: even dependent claim 39 indicates that it uses an additional oil-in-water adjuvant, not just an oil-in-water carrier.

Applicants therefore respectfully request withdrawal of the rejection under 35 U.S.C. 103(a).

Applicant believes that all pending rejections have been addressed and that the present application is now in condition for allowance. Favorable reconsideration and allowance of the pending claims is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

Date 10 April 2008 By 

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